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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/500,700	02/09/00	BARBAS III	C	SCRIP1160-4

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	4

DATE MAILED: 05/23/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/500,700	Barbas, et al.
Examiner	**Group Art Unit**
Gerald G. Leffers Jr.	1636

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers, no CRF was filed, no paper sequence was filed for those sequences and no attorney statement was filed for those sequences. These sequences include sequences listed throughout the specification (e.g. the zinc finger-nucleotide binding motif and amino acid sequence TGEKP given on page 51, lines 16-24) and the sequences given in many of the figures (e.g. Figures 1 and 2). If the Sequence Listing required for the instant application is identical to that of another application, and covers the sequences specified above, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP 2422.02).

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. *Any* response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 09/500,691. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims specify an isolated zinc finger-nucleotide binding polypeptide variant comprising a specified number of zinc finger modules that bind to a cellular nucleotide sequence

and modulate the function of the cellular nucleotide sequence. The claims only differ in the number of zinc finger modules specified, with claim 1 of Application No. 09/500,691 specifying at least 2 zinc finger modules and the instant application specifying at least 4 such modules. The instant claim is thus narrower in scope, but totally encompassed by claim 1 of Application No. 09/500,691. The invention of the instant application is an obvious variant of the invention of Application No. 09/500,691 because it is and was known in the art that the number of modules which interact with the target nucleotide sequence can affect the specificity of the protein/nucleic acid interactions. One would have been motivated to construct zinc finger-nucleotide binding protein variants having four modules which interact with a target nucleotide sequence in order to achieve the expected benefit of altering the specificity with which the polypeptide variants bind target nucleic acid sequences. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is an isolated zinc finger-nucleotide binding protein variant comprising at least four zinc finger modules that bind to a cellular nucleotide sequence and modulate the function of the cellular nucleotide sequence.

The specification defines a variant zinc finger-nucleotide binding protein (ZFBP) as "..a polypeptide which is a mutagenized form of a zinc finger protein or one produced through recombination. A variant may be a hybrid which contains zinc finger domain(s) from one protein linked to zinc finger domain(s) of a second protein, for example. The domains may be wild type or mutagenized. A "variant" or "derivative" includes a truncated form of a wild type zinc finger protein, which contains less than the original number of fingers in the wild type protein." (page 10, line 16). The claim does not limit the source of the variant to any one zinc finger-nucleotide binding protein. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to a polypeptide of the instant invention. Nor does the specification or the claim appear to limit such alterations to just the zinc finger domains within the zinc finger-nucleotide binding protein. Thus, the claim encompasses any mutation within any portion of any zinc finger binding protein (having 4 zinc finger modules which interact with a nucleic acid sequence) which renders it a "variant", or even any combination of zinc finger modules from any known or unknown ZFBPs, so long as the

"variant" ZFBP retains its ability to bind to a cellular nucleotide sequence and modulate its activity. Therefore, the claim is a very broad genus claim.

While a structural feature recognized in the art is common to all of the members of the claimed genus (i.e. the zinc finger module), there is little guidance in the specification as to the exact structure of a "variant" which retains its ability to bind a particular nucleotide sequence as well as its non-nucleic acid binding function (e.g. transactivation, dimerization, etc.) beyond those described for two known zinc finger proteins, TFIIIA and zif268. There is little description within the specification as to what modifications to make to any other zinc finger protein known in the art which will not abolish its ability to bind a particular DNA sequence and will not affect its other functions. There is no description at all in the specification with regard to alterations within non-finger domains (e.g. dimerization, activation or repressor domains) for any zinc finger protein that will allow the polypeptide to retain its ability to bind a particular DNA sequence and modulate its function. Because the claimed genus is so broad and so highly variant as to what alterations are permissible in order to make a "variant" or "derivative", because it is difficult to accurately predict the effects of alterations in primary sequence on a protein's structure/function and because of the lack of guidance from the specification as to what alterations are possible for the general class of zinc finger-nucleotide binding proteins in any domain of such proteins which would allow the protein to retain the ability to bind a particular nucleic acid sequence and modulate its activity, the common feature of the members of the genus, the zinc finger modules, is not sufficient in and of itself to allow one of skill in the art to envision a representative number

of all the potential variants which retain the ability to bind a particular nucleotide sequence and modulate its function. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicants were not in possession of the claimed genus.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the term "variant" are unclear. It is unclear as the claim is written as to whether the term reads on "natural" variants of a zinc finger-nucleotide binding protein (ZFBP) which differ in some manner from the "wild type" zinc finger-nucleotide binding protein. For example, would a single amino acid change in one species of organism in one of the zinc finger motifs of a conserved zinc finger-polynucleotide binding protein relative to the "consensus" wild type sequence constitute a "variant"? Would a single amino acid change in a domain of such a zinc finger-polynucleotide binding protein outside of the zinc finger domains constitute such a variant, derived naturally or otherwise? Upon reading the specification it appears that applicants intend for the term to mean

a ZFBP which has been modified by mutagenesis (e.g. random or site directed mutagenesis, truncation or deletion) so that it differs from the "wild type" protein. It would be remedial to amend the claim to clearly indicate whether the term "variant" reads on natural variants of a conserved zinc finger-polynucleotide binding protein and whether a single amino acid change within any domain of the zinc finger-polynucleotide binding protein would satisfy the requirement of being a "variant".

Claim 1 is also vague and indefinite in that the metes and bounds of the phrase "..modulate the function of the cellular nucleotide sequence." are unclear. The function of a binding site is to bind its cognate binding protein. It is unclear then how the binding of the zinc finger-nucleotide binding protein variant will affect the "activity" of its binding site. Upon reading the specification, it appears applicants intend to mean that the binding of the zinc finger-nucleotide binding protein variant to its cognate binding site results in modulation of a functional characteristic of the nucleotide sequence associated with the binding site (e.g. an RNA featuring such a binding site or a DNA comprising such a binding site associated with a coding sequence). It would be remedial to amend the claim to clearly indicate that the functional nucleic acid sequence that is modulated is not the binding site itself per say, but a functional characteristic of the nucleic acid sequence with which it is associated.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The specification does not disclose any specific and substantial utility for the claimed invention, credibility will not be assessed.

The claimed invention is an isolated zinc finger-nucleotide binding polypeptide variant comprising at least four zinc finger modules that bind to a cellular nucleotide sequence and modulate the function of the cellular nucleotide sequence. The specification asserts that the isolated polypeptides of the instant invention have utility as sequence-specific modulators of a nucleic acid function. The specification also asserts that the isolated zinc finger-nucleotide binding protein (ZFBP) variants of the instant invention can enhance transcription of structural genes within an organism when they possess an activation domain fused to the DNA-binding domain by binding a cognate binding site within the promoter region of the gene. The specification further asserts that the isolated ZFBP variants of the instant invention can inhibit transcription of a gene by competitive inhibition with a wild type ZFBP at a site where the wild type protein normally activates or enhances transcription of the gene, or by binding to a site within the gene itself to directly inhibit transcription by the polymerase. The specification also contends that the ZFBP polypeptides of the instant invention can inhibit translation of a given

RNA by specifically binding the RNA and inhibiting translation. It is also asserted that the isolated polypeptides of the instant invention can be used to generate antibodies specific for the particular ZFBP, which can then be used to detect the ZFBP or to inhibit its activity in cells. Finally, the specification also asserts that because the ZFBP of the instant invention can bind specifically to DNA and inhibit or enhance gene transcription, the isolated polypeptide variants of the instant invention can be used for treatment of diseases such as cell proliferative disorders (e.g. cancer).

A utility for an isolated variant of a zinc finger-nucleotide binding protein having at least 4 zinc finger modules which interacts with a polynucleotide sequence is not well established in the art. Although the specification teaches examples of where variants of a ZFBP polypeptide having at least four modules which interact with a particular nucleotide sequence can inhibit or enhance transcription of a reporter gene, in vitro or in vivo, the specification does not provide teachings of where such an isolated ZFBP variant is specific for a particular gene whose regulation has substantial utility. The assertion that the isolated polypeptides of the instant invention can be used to treat cell proliferation disorders is not specific in that no particular gene associated with any one of the many cell proliferative disorders (e.g. one of the may forms of cancer having different etiologies) is specified. Likewise, the assertion that one can form antibodies against a particular, isolated ZFBP variant having at least four modules which interact with a particular nucleotide sequence is not a specific utility in that no example is taught wherein a particular ZFBP polypeptide is associated with a gene target whose regulation has substantial

utility. Therefore, the claimed invention of an isolated zinc finger-nucleotide variant having at least four modules which interact with a particular sequence is not considered to have a well established, specific or substantial utility.

Claim 1 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hanas et al (U).

Hanas et al teach the construction and isolation of mutants of TFIIIA which either lack the fourth zinc finger of TFIIIA (page 9862; Figure 1A) or comprise a fusion of the 7th and 8th zinc fingers of the protein (page 9862; Figure 1B). Hanas et al further teach that both of the

mutants retain the ability to bind their cognate binding sequence and influence transcription of a 5S RNA gene in Xenopus unfertilized egg extracts (Abstract; page 9866; Figures 4 and 5).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Crozatier et al (V).

Crozatier et al teach the isolation of four mutants in the serendipity δ (*sry δ*) zinc finger protein of Drosophila. Crozatier et al teach that three of the four mutations in *sry δ* (*sry* δ^{2}, *sry*

δ^{SF1} and *sry δ^{SF2})* are localized to the third zinc finger module (out of seven) of the protein (Abstract; page 914, column 1). That polypeptides of these proteins retain some ability to bind DNA and affect its function is evident from the teaching of Crozatier at all that the mutants can complement one another (Table 1; page 915, column 1) and that the mutations apparently affect the transcription of different sets of genes at different stages of development (page 915, column 1, paragraph 2). Crozatier et al teach that in vitro experiments to determine the consequences of the *sry δ^{4}*, *sry δ^{SF1}* and *sry δ^{SF2}* mutations on the ability of the encoded polypeptide to specifically bind DNA were in progress at the time of publication (page 915, column 1, paragraph 1).

Crozatier et al do not specifically teach the isolation of the mutant proteins.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express and purify the polypeptides encoded by the *sry δ^{SF1}* and *sry δ^{SF2}* genes because Crozatier et al teach that such isolation of the mutant proteins was possible at the time the invention was made and because recombinant techniques are and were well known in the art for producing and isolating desired DNA-binding polypeptides. One would have been motivated to do so in order to achieve the expected benefit of performing in vitro analysis of the DNA-binding properties of the mutant proteins relative to the wild type protein, as suggested by Crozatier et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in isolating the mutant *sry δ^{SF1}* and *sry δ^{SF2}* encoded polypeptides described by Crozatier et al for in vitro analysis of their DNA-binding properties.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GLJ

G. Leffers, Jr.
Patent Examiner
Art Unit 1636

TERRY MCKELVEY
PRIMARY EXAMINER

May 22, 2000